Rork *et al.* is alleged to teach sustained-release formulations comprising an active agent core and a film coating, the core being made of (a) diethylisovaleramide or bromo-isovaleryl-urea, and (b) a polymer that forms gel beads upon hydration and dissolves slowly (specifically sodium acrylate or carboxymethylene), and the film coating being made of, *inter alia*, ethyl cellulose or cellulose acetate. The term "acceptable amide of isovaleric acid" in applicant's claim 1 is alleged to read on diethylisovaleramide.

Balandrin *et al.* is alleged to teach the use of an isovaleramide tablet, capsule, or drop, for treating CNS disorders.

The examiner alleges that one of skill in the art would be motivated to use the isovaleramide tablets of Balandrin *et al.* or the diethylisovaleramide of Rork *et al.* in the sustained-release composition of Rork *et al.* with an expectation to prolong the compounds' therapeutic effects taught by Balandrin *et al.*. The examiner alternatively alleges that it would have been obvious to use the sustained-release formulation of Rork *et al.* with the isovaleramide of Balandrin *et al.* in order to provide a sustained-release of isovaleramide for a prolonged treatment of CNS disorders such as anxiety or restlessness.

Applicant's Response

Applicants respectfully traverse the examiner's rejection and submit that the examiner has failed to make out a *prima facie* case of obviousness. A *prima facie* case of obviousness requires, *inter alia*, that the examiner point to some motivation in the prior art for making the claimed combination. The examiner has failed to do so.

A. Amendment of claims 1,19, and 24

The examiner considers the term "acceptable amide of isovaleric acid" in claim 1 to read on diethylisovaleramide. To avoid confusion as to the chemical structure of the compound claimed, claims 1, 19, and 24 have been amended to replace this term with the term "isovaleramide."

B. Balandrin *et al.*

First, applicants agree with the examiner that Balandrin *et al.* teaches the efficacy of isovaleramide and related compounds as anxiolytic and sedative agents.

Balandrin *et al.* is *silent*, however, with regard to the *duration* of the anxiolytic or sedative effects of isovaleramide, or how long an effect is even desired. Without this knowledge, which is clearly lacking in Balandrin *et al.*, one of skill in the art would not consider a sustained-release isovaleramide tablet to be either beneficial or desirable. Thus, Applicants respectfully submit that Balandrin *et al.* does not suggest the desirability of a sustained-release formulation of isovaleramide and related compounds and would not motivate one of skill in the art to make that formulation.

Indeed it is *Applicants' instant application* which teaches that "orally administered isovaleramide has a short half-life in humans.... [T]he short half-life requires that isovaleramide be administered frequently to sustain a therapeutic concentration of the drug without adverse effects." It is the *instant application* that teaches the short duration of isovaleramide's effects, due to its short half-life, the problem with the simple tablets described in Balandrin *et al.*, and the desirability of the instant formulation. Applicants, therefore, respectfully submit that the examiner has found the *motivation or suggestion* to make a sustained-release formulation of isovaleramide by *hindsight*, using applicants' own disclosure as a roadmap or template.

C. Rork *et al.*

Applicants agree with the examiner that Rork *et al.* teach a "controlled" or "sustained" release tablet of pharmaceutically active ingredients. The novelty of Rork *et al.*, however, lies in the discovery of the utility the particular combination of (a) a core of active agent and polymer beads that gel upon hydration, and (b) a film coating with apertures that provide an area for the hydration and release of the gel "beads" for improved sustain-release of the active compounds contained therein.

Rork *et al.* was clearly directed to the sustained-release formulation generically, rather than the formulation with any particular drug. Rork *et al.* broadly asserts that the disclosed sustained-release tablet could be used with "any compound commonly referred to as a 'drug,'" col. 5, ll. 18-19, and lists more than *a hundred* drugs, including "hynotics and sedatives such as amides and ureas, exemplified by diethylisovaleramide and alpha-bromo-isovaleryl urea." *without discrimination*, col. 5-7, and *without specifying why such a sustained-release tablet is desirable for those drugs*. The only sustained-release tablets *actually made* or *claimed* by Rork *et al.* contain lovastatin, nifedipine, and simvastatin—all heart-disease drugs and clearly different from the compounds in applicants' formulations.

Applicants respectfully submit that Rork *et al.*'s generic and broad disclosure to sustained-release formulations, without more, would not motivate one of skill in the art to make a sustained-release tablet for the compounds claimed in applicants' formulations. If so, a sustained-release formulation for *every* drug would be rendered obvious by Rork *et al.*, for there is nothing in Rork *et al.* that particularly directs one of skill in the art to applicants' compounds more than any other compounds. Rork is simply too general in its teachings.

Applicants submit that the necessary predicate for making a sustained-release formulation for a drug is that the chemical and metabolic properties of the compound, such as its half-life when injested, and the nature of the compound's pharmaceutical use, are such that a sustained-release formulation would be beneficial and desirable. Rork *et al.* does not teach anything about the properties or use of the compounds in applicant's claimed formulations, and thus would not motivate one of skill in the art to make a sustained-release formulation containing them.

As discussed above, it is Applicants' *own* disclosure which teaches the short half-life of the compounds, and that it is the short half-life of the compounds after ingestion that requires that the compounds to be frequently administered to sustain a therapeutic concentration without adverse effects.

The examiner has arrived at the obviousness of the claimed formulations by hindsight.

It is respectfully submitted that Applicant's claimed invention is not obvious over any combination of Rork *et al.* and Balandrin *et al.* and therefore, withdrawal of this ground for rejection is courteously requested.

II. The Rejection over Balandrin *et al.* in view of Rork *et al.* and Pankhania *et al.*

Claims 6, 12, 13, 21, and 28 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Rork *et al.*, U.S. Patent No. 5,582,838, in view of Balandrin *et al.*, U.S. Patent No. 5,506,268, and further in view Pankhania *et al.*, U.S. Patent No. 5,415,871.

Pankania *et al.* is alleged to teach xantham gum as a gelling agent in sustained-release formulations for pharmaceutically active agents such as sedatives, and is admittedly not described in Balandrin *et al.* or Rork *et al.* The examiner alleges that it would have been obvious to use xantham gum as the gel forming polymer taught by Rork *et al.*, containing diethylisovaleramide or isovaleramide taught by Rork *et al.* and Balandrin *et al.*

Applicants' Response

Applicants respectfully traverse the examiner's rejection and submit that the examiner has failed to make out a *prima facie* case of obviousness for the reasons stated above. Balandrin *et al.* and Rork *et al.* do not render obvious the claimed sustained-release formulations because neither specifically suggests the desirability of a sustained-release formulation for the compounds specifically claimed. Pankania *et al.*'s teaching regarding Xantham gum's utility as a gelling agent also does not supply the necessary motivation to make the claimed combination.

It is respectfully submitted that Applicant's claimed invention is not obvious over any combination of Rork *et al.*, Balandrin *et al.*, and Pankania *et al.*, and therefore, withdrawal of this ground for rejection is courteously requested.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date May 20, 2002 By _____

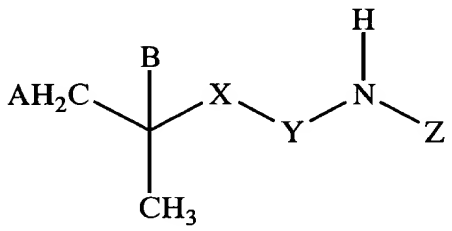
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

Marked Up Version to Show Changes Made

1. (Once Amended) A pharmaceutical composition, comprising a therapeutically effective amount of an active compound in a sustained-release formulation, wherein said active compound is selected from the group consisting of:

isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, [a pharmaceutically acceptable amide of isovaleric acid] isovaleramide, a compound having the structure:



wherein A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

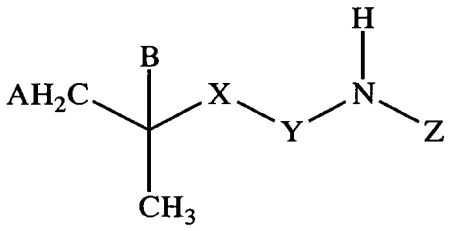
Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

19. (Once Amended) A process for preparing a sustained-release pharmaceutical composition which contains a therapeutically effective amount of

an active compound, comprising mixing together a therapeutically effective amount of an active compound with one or more substances that act to sustain release of the compound, wherein the active compound is selected from the group consisting of:

isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, [a pharmaceutically acceptable amide of isovaleric acid] isovaleramide, an active compound having the structure:



wherein A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

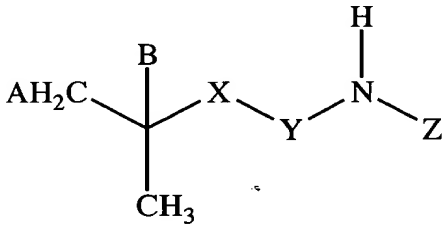
Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate, with the proviso that the treated pathology is not convulsions when the compound is 3-methylisovaleramide, isopropyl carbamate, or isobutyl carbamate.

24. (Once Amended) A method of treating a pathology that is ameliorated by a modulation of CNS activity, comprising administering to a

patient suffering from said pathology a pharmaceutical composition comprising a therapeutically effective amount of a sustained-release formulation, wherein the active compound is selected from the group consisting of: isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, [a pharmaceutically acceptable amide of isovaleric acid] isovaleramide, an active compound having the structure:



wherein A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate, with the proviso that the treated pathology is not convulsions when the compound is 3-methylisovaleramide, isopropyl carbamate, or isobutyl carbamate.